Heterocyclic Letters
Vol. 6| No.1|11-14| Nov-Jan| 2016
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

2,4-DIHYDROXY-3-(INDOL-2-)-YL-QUINOLINE VIA A SUBSTANTIAL METHODOLOGY – FISHER INDOLE SYNTHESIS

P. Pitchai,[1]* A. Nepolraj,[1]M. Sathiyaseelan[1] and R. M. Gengan[2]

[1]*PG and Research Department of Chemistry, Government Arts College (Auto), Kumbakonam 612 001, TN, India*
[2]*Department of Chemistry, Steve Biko Campus, Durban University of Technology, Durban 4000, South Africa*
**E-mail: pitchaipandian@gmail.com*

Abstract:
Fisher indole methodology, a simple application was used to generate indole as a substitution on the quinoline ring. Conventional heating and microwave irradiation was compared. The ease of work-up procedure, reduced time and moreover the high yield is exceptional however microwave irradiation presented more advantages.

Keywords: Indole, quinoline, Fisher-indole method, 3-acyl-2,4-dihydroxyquinoline.

Introduction:

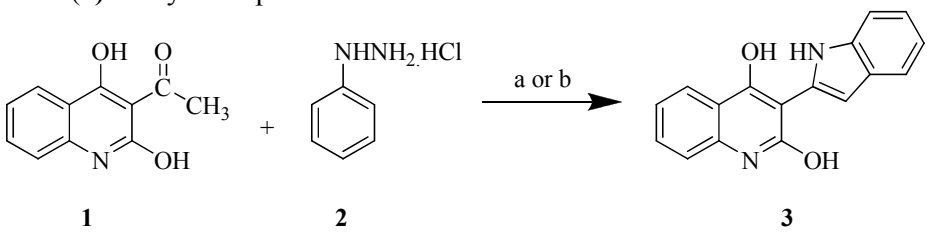
Our earlier investigations to synthesize indoloquinoline alkaloids *via* synchronized methodologies such as photochemical[i-iii], microwave[iv], Fisher-indole[v,vi], Bucherer[i], Vilsmeier-Haack[vii] and Claisen condensation[vii] are reported. The importances of indole and quinoline alkaloids are thoroughly exemplified in our earliest publications[i-vii]. The Fischer indole methodology is one of the most important processes in heterocyclic chemistry, leading to a large variety of hetero-polycyclic biologically active compounds containing the indole nucleus and in some cases is the only method available for reaching target structures. This has led to our aim of fabricating novel indole-substituted quinoline by applying Fisher-indole procedure.

The effects of acid catalysts and temperature in the uncatalyzed reaction on the direction of cyclization of unsymmetrical ketone phenylhydrazones in the Fischer indole synthesis had been examined thoroughly by Miller et al[viii]. Conversion of arylhydrazones into indoles with acid catalysts such as glacial acetic acid[viii,ix], concentrated sulfuric acid[viii,x], *p*-toluenesulphonic acid[viii,x], and polyphosphoricacid[viii,x,xi], are reported in the Fisher indole synthesis. Lewis acids[viii,x] like $ZnCl_2$, $AlCl_3$ and PCl_5 and metal acetates[x] like $Pd(OAc)_2$ are also employed to increase yields. Some organometallic catalysts[x] and microwave irradiation[x] are also used for the enhancement of yield.

Results and discussion:

We chose 3-acyl-2,4-dihydroxy quinoline(**1**) as a starting precursor since its synthetic procedure is clearly exposed in our earlier report. In synthesizing 2,4-dihydroxy-3-(indol-2-)-yl-quinoline(**3**), compound(**1**) was dissolved in dry methanol and an equimolar amount of

phenylhydrazine hydrochloride was added followed by *p*-toluene sulphonic acid as catalyst; the latter was chosen since it was easily accessible. After six-hour of refluxing in a steam bath, thin layer chromatography displayed the highest conversion of substrates to the product. After usual work-up, followed by column chromatography purification with the mobile phase of petroleum ether and ethyl acetate (40:60), afforded 75% yield of 2,4-dihydroxy-3-(indol-2-)-yl-quinoline(**3)** as a yellow powder.



1 **2** **3**

Scheme 1. Synthesis of 2,4-dihydroxy-3-(indol-2-)-yl-quinoline **3**: a) *p*-TSA, MeOH, 70°C, 6 hr; b) *p*-TSA, MWI, 300 watts, 110°C, 3 m.

In our earlier reports[v,vi] with other substrates and reactions we showed that condensation occurred at 4th position of the quinoline ring however this current workshows otherwise. Herein the α-hydrogen to the carbonyl carbon is acidic and easily tautomerizes into its enolic form thereby making the mixture acidic in a polar protic solvent. Moreover the third position on the quinoline ring is already occupied and there is no acidic proton available to involve in any other keto-enoltautomerism with the hydroxy group on fourth position of quinoline ring.

The infra-red spectrum of **3** showed absence of the ketonic carbonyl C=O stretching at 1664 cm^{-1}which was present in **1** however the newly formed C=N stretching at 1617 cm^{-1} is presented and confirms the functional group transformation. In the^{1}H NMR spectrum, the characteristic chemical shift at δ 11.18 and 16.00 is observed for hydroxyl hydrogen.

The ^{13}C NMR further supports the structure; the ketonic carbon at δ 192 and the aliphatic carbon at δ 27 which is present in **1** is lacking in the spectrum of **3**. Furthermore, although the signals of the 2nd and the 4th carbon of quinoline were retained, there was a marginal change in their chemical shift value thereby confirming two hydroxyl groups were unaffected by the reaction conditions.

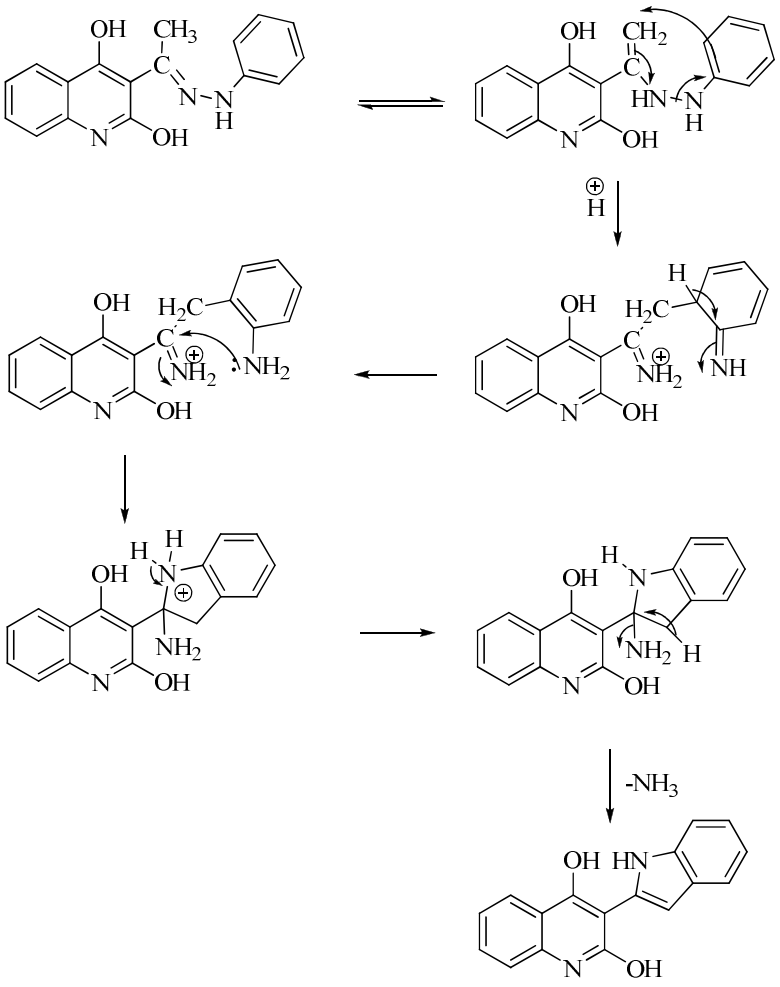


Figure I: Fischer-indole mechanism of formation of 2,4-dihydroxy-3-(indol-2-)-yl-quinoline **3**

After confirming the structure by simple spectroscopic techniques, the reaction was conducted with a synthetic microwave set at 300 watts and reaction temperature of 130°C; no solvent was used. This reduced the reaction time from 6 hours to 3 minutes. The yield was quite increased about 5% by comparing with the conventional procedure.

Conclusion:

The Fisher-indole protocol was used to synthesize novel 2,4-dihydroxy-3-(indol-2-)-yl-quinoline; which is consider to be an ever classic method to seal the indole ring; microwave irradiation reduced the reaction time from 6 hours to 3 minutes and enhanced the yield considerably.

Experimental:

General

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrophotometer as potassium bromide discs unless otherwise indicated. ^{1}H NMR spectra were obtained on a Brucker (400 MHz) instrument in $CDCl_3$ solutions using tetramethylsilane as an internal standard. *J* Values are given in Hz. Mass spectra were obtained at the Vellore Institute of Technology, Vellore, Tamil Nadu, India. Column chromatography utilised Merck silica gel 60 and hexane and ethylacetate as eluants. All the

basic chemicals were purchased from Merck (India) and Fluka (South Africa). The microwave used is a CEM microwave synthesizer.

Synthesis of 2,4-dihydroxy-3-(indol-2-)-yl-quinoline(3)

a)Conventional method

A mixture of 3-acyl-2,4-dihydroxyquinoline (**1)** (2.03 g, 1 mmol) and phenylhydrazine hydrochloride (**2)** (1.23 g, 1 mmol) was dissolved in methanol; a pinch of *p*-TSA was added and refluxed for 6 hours. After completion of reaction (monitored by TLC), the reaction mixture was added to ice cold water. The solid product obtained was filtered, dried and purified through column chromatography with the mobile phase ethylacetate : petroleum ether (40:60).

b)Microwave method

A mixture of 3-acyl-2,4-dihydroxyquinoline (**1)** (2.03 g, 1 mmol) and phenylhydrazine hydrochloride (**2)** (1.23 g, 1 mmol) was mixed to form a paste to which *p*-TSA was added and thoroughly mixed. It was introduced in a CEM microwave synthesizer for 3 min at 300 watts and 110°C. After work-up and column purification the yield is found to be same as conventional method.

Preparation of 2,4-dihydroxy-3-(indol-2-)-yl-quinoline (3)

Color: light yellow,yield: 75% (conventional) & 80% (microwave), M.p.: 192°C, GC-MS: *m/z %*: 276 (20) $[M]^+$. FT-IR(KBr pellet, υ_{max}/cm^{-1}): 3453 υ(quinC_2-O-H), 3323 υ(indol-N-H), 1671 υ(quin-C_4=O) and 1593 υ(quin-C=N), ^{1}H NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 6.97 (s, 1H, N-H), 7.16-7.18 (d, 1H, J = 8 Hz, qui-C_5-H), 7.41-7.45 m, 2H, indol- C_3-H, C_4-H& C_5-H), 7.55-7.60 (m, 5H, qui-C_6-H, C_7-H, C_8-H & ind- C_6 & C_7-H), 11.18 (bs, 1H, O-H), 16.00 (bs, 1H, O-H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz, δ ppm): 172.87 (qui-C_4), 161.44 (qui-C_2), 150.89, 149.12, 141.91, 140.20, 137.91, 134.71, 132.27, 129.96, 127.20, 122.67, 117.00, 116.75, 111.32, 110.54 (Ar-C).

Acknowledgement

The authors thank DST-SERB, India and NRF (South Africa) for funding this work, Annamalai University,Chidambaram for providing NMR analysis and VIT, Vellore for GC-MS analysis.

References

i. T. Dhanabal, R. Sangeetha, P. S. Mohan,Tetrahedron.62, 6258(2006).
ii. R. Nandhakumar, T. Suresh, P. S. Mohan, TetrahedronLett.43,3327 (2002).
iii. P. Pitchai, P. S. Mohan, R. M. Gengan,Indian J. Chem.48B,692 (2009**)**.
iv. R. M. Gengan, P. Pitchai, K. Chandraprakash, P. S. Mohan,Molecules.15,3171 (2010).
v. T. Dhanabal, R. Sangeetha, P. S. Mohan,Tetrahedron Lett.46, 4509 (2005).
vi. P. Pitchai, C. Uvarani, T. R. Makhanya, R. M. Gengan, P. S. Mohan, Res. & Revs: Journal of Chem. 3, 60(2014).
vii. P. Pitchai, M. Sathiyaseelan, A. Nepolraj, R. M. Gengan,Indian J. Chem.54B, 1290 (2015).
viii. F. M. Miller, N. W. Schinske,J. Org. Chem.43, 3384 (1978).
ix. R. Sheng, L. Shen, Y. Q. Chen, Y. Z. Hu,Synth.Commun.39, 1120 (2009).
x. W. G. Gordon,J. Chem. Soc. Perkin Trans.1, 1045 (2000).
xi. I. S. Chikvaidze, N. N. Barbakadze, S. A. Samsoniya. Arkivoc.6,143 (2012).

Received on January 7, 2016.